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Effects of Ambient Sulfur Oxides and Suspended Particles on Respiratory Health of Preadolescent Children

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16. ABSTRACT
This paper reports results from an ongoing study of outdoor air pollution and respiratory health status of children living in six cities in the eastern and mid-western United States. The study enrolled 10,106 white preadolescent children between 1974 and 1977 in three successive annual visits to each city. Each child received a spirometric examination and a parent completed a standard questionnaire. Of this cohort, 8,380 children were seen for a second examination one year later. An air pollution monitoring program was begun in each community at about the time of the first examination. For this report, measurements of Total Suspended Particulates (TSP), the sulfate fraction of TSP (TSO_4), and sulfur dioxide (SO_2) concentrations at study-affiliated outdoor stations were combined with measurements at other public and private monitoring sites to create a record of TSP and SO_2 concentrations in each of 9 air pollution regions during the one-year period preceding each examination and, for TSP, during each child's lifetime up to the time of testing.
Follow-up of these children is continuing, and analyses of the longitudinal health data along with the more extensive aerometric data collected in later years will aid in the interpretation of these results.

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JOURNAL ARTICLE

Effects of Ambient Sulfur Oxides and Suspended Particles on Respiratory Health of Preadolescent Children[1-3]

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SUMMARY Reported here are the results from an ongoing study of outdoor air pollution and respiratory health of children living in six cities in the eastern and midwestern United States. The study enrolled 10,106 white preadolescent children between 1974 and 1977 in 3 successive annual visits to each city. Each child received a spirometric examination, and a parent completed a standard questionnaire. Of this cohort, 8,380 children were seen for a second examination 1 yr later. An air pollution monitoring program was begun in each community at about the time of the first examination. For this report, measurements of total suspended particulates (TSP), the sulfate fraction of TSP (TSO_4), and sulfur dioxide (SO_2) concentrations at study-affiliated outdoor stations were combined with measurements at other public and private monitoring sites to create a record of TSP, TSO_4, and SO_2 concentrations in each of 9 air pollution regions during the 1-yr period preceding each examination and, for TSP, during each child's lifetime up to the time of testing. Across the 6 cities, frequency of cough was significantly associated with the average of 24-h mean concentrations of all 3 air pollutants during the year preceding the health examination ($p < 0.01$). Rates of bronchitis and a composite measure of lower respiratory illness were significantly associated with average particulate concentrations ($p < 0.05$). In analyses restricted to lifetime residents, these outcomes were significantly associated with measures of lifetime mean TSP concentration. Within the cities, however, temporal and spatial variation in air pollutant concentrations and illness and symptom rates were not positively associated. Early childhood respiratory illness history of lifetime residents was not consistently associated with average TSP concentrations during the first 2 yr of life. Pulmonary function parameters (FVC and FEV_1) were not associated either with pollutant concentrations during the year preceding the pulmonary function test or, for lifetime residents, with lifetime average concentrations. These results suggest that, for preadolescent children, exposure to moderately elevated concentrations of pollutants believed to be representative of emissions from combustion of fossil fuels increases risk for bronchitis and some other respiratory disorders, but has little or no effect on pulmonary function level. The strong association between TSO_4 concentrations and other measures of ambient fine particle concentration implies that these results are relevant to the health effects of fine particulate air pollution. Follow-up of these children is continuing, and analyses of the longitudinal health data, along with the more extensive aerometric data collected in later years, will aid in the interpretation of these results.

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Introduction

Despite widespread public concern about the health effects of sulfur oxide and particulate air pollution, there is substantial uncertainty regarding the effects of these pollutants at concentrations typical of the contemporary United States. The epidemiologic data base consists in large part of studies conducted in communities with substantially higher air pollutant concentrations than are common in the United States today (1, 2). Moreover, these studies often used measures of exposure, such as Coefficient of Haze or British Smoke, that are not directly related to measures routinely used in this country.

The Harvard Study of Air Pollution and Health was begun in the fall of 1974 to provide a contemporary source of epidemiologic data regarding the health effects of the principal constituents of fossil fuel air pollution. Air pollution monitoring and health data collection were begun in 6 cities in the eastern and midwestern United States (Watertown, MA; Kingston and Harriman, TN: Steubenville and Mingo Junction, OH; St. Louis, MO; Portage, WI and surrounding towns; Topeka, KS) between the fall of 1974 and the spring of 1977. Random samples of adults and preadolescent school children were enrolled in each city. The children were enrolled at three successive annual visits to each city and then seen annually for spirometric examination, measurement of height and weight, and completion of a standardized respiratory symptom questionnaire. Participating adults were enrolled during the first visit to each city and then seen at 3-yr intervals (3).

This report describes the association between respiratory health of children as measured by reported history of respiratory illnesses and symptoms and levels of pulmonary function at their first and second examinations, and outdoor concentrations of total suspended particles (TSP), sulfur dioxide (SO_2), and, to the extent measurements are available, the sulfate fraction of TSP (TSO_4) in each city during the years preceding these examinations. Three periods of exposure are considered: the 1-yr period preceding an examination, the child's lifetime up to the date of examination, and the first 2 yr of life. Analyses based on the latter 2 periods are limited to lifetime residents. This report focuses on TSP, TSO_4, and SO_2 concentrations because these were the only pollutants consistently monitored prior to and during the early years of the study. TSO_4 measurements are of special interest because of the current regulatory emphasis on fine particulate air pollution (4) and because of the

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high correlation between TSO_4 concentrations and other measures of fine particulate air pollution (5).

Methods

Sample Selection

The characteristics of the children participating in the study have been described elsewhere (6). Briefly, the objective was to enroll first and second grade children in each city. In the larger cities, a geographically defined area (St. Louis, MO) or a subsample of schools (Topeka, KS) was identified for study. In Portage, WI, a smaller community, children from surrounding areas and from grades up to and including the fourth were included. Children enrolled at the first visit to each city were subsequently reexamined annually, and new first graders were entered until 1,500 to 2,000 children had been recruited in each city. For this report, the population under study was defined as all white children enrolled during 1 of the first 3 visits to each city who were 6 through 9 yr of age at the initial visit.

Air Monitoring

Air pollution monitoring stations were established in residential areas in Watertown, MA, Kingston, TN, Topeka, KS, and St. Louis, MO, at about the time of the first health interview. In Steubenville, OH, and Portage, WI, we cooperated with local authorities to expand and upgrade established monitoring programs. Air quality monitoring at study-affiliated stations included measurement of TSP, SO_2, nitrogen dioxide (NO_2), ozone (O_3), size-fractionated suspended particulates, and water-soluble sulfates (TSO_4). By 1978, all air monitoring stations participating in the study, including those of cooperating local authorities, were fully operational and participating in a quality assurance program that included an annual independent audit sponsored by the United States Environmental Protection Agency. Before 1978, however, only TSP and SO_2 concentrations were consistently available from the study-affiliated stations and from the other public and private stations operating in the study areas. TSO_4 measurements were available from a subset of these stations.

The air pollution data base for this report consists of all TSP, TSO_4, and SO_2 measurements collected at the study-affiliated sites or at other sites in the study communities participating in the National Ambient Air Quality Data Bank (7). A list of the monitoring stations providing data is available from the writers on request.

At all stations, 24-h mean TSP concentrations were measured by high volume samplers in accordance with recommended sampling procedures (8). The water-soluble sulfate fraction also was measured using standard methods (9). At some stations, 24-h mean SO_2 concentrations were measured by West-Gaeke bubblers (10). Other stations contributing to the data base used continuous SO_2 analyzers. The continuous analyzers used methods equivalent to federal reference methods of the EPA. These analyzers produce a sequence of 1-h mean concentrations. For these stations, 24-h mean values were calculated as the average of the 1-h values, provided that at least 18 1-h values were recorded.

The 24-h mean values were reviewed for consistency and completeness. Questionable values were identified by comparing individual and monthly mean values across stations located in each community and over time for a single station. The original data records were examined for questioned observations. Inconsistent observations were verified or corrected whenever possible and otherwise eliminated from further analysis.

Nine air pollution regions were defined by dividing each of 3 cities: St. Louis, MO, Steubenville, OH, and Kingston-Harriman, TN, into 2 regions and treating the other 3 cities as single regions. In Steubenville and Kingston-Harriman, regions were defined by topographic features and by the location of major air pollution sources. In St. Louis, the 2 regions were defined by proximity to the major source of SO_2. Measurements at multiple outdoor stations within the study communities showed that variation in pollutant concentrations within these 9 regions was smaller than between-region variability (11, 12). Therefore, air pollutant concentrations for each sampling day were estimated by the mean overall stations in the region with values recorded for that day.

To link the air pollution and health data, we assigned children to the air pollution region containing their school. The 3 cohorts (years of enrollment) of children enrolled in each of the 9 regions defined 27 groups of children with different histories of exposure to outdoor air pollution in the years preceding their first and second examinations. Three exposure periods were considered in the health effects analysis. The first of these was the 1-yr period preceding the examination. Each examination was assigned to a quarter of the year, and the exposure year was defined as the 4 quarters ending with that quarter. The 1-day values were averaged in each quarter, and the annual mean concentration was estimated by the average of the 4 quarterly means. The 1-day values were aggregated over the entire year for estimation of the ninetieth percentile. Second, for all children who were lifetime residents of their region, quarterly mean values were averaged over all quarters from the child's date of birth to the date of the health examination of interest. Finally, for the same children, we calculated the mean value for the 8 quarters following the date of birth.

Total suspended particulates measurements were available for all region-cohorts and exposure periods. Sulfur dioxide measurements were available only for the years immediately preceding the health examinations, and no SO_2 measurements were available for the first examination period in the Ridge area of Steubenville. TSO_4 measurements were available for the preceding year in 5 of the 6 cities. In Portage, the city with the lowest particulate concentrations, TSO_4 concentrations were estimated by extrapolation from mean concentrations in subsequent years. Because of the more limited availability of TSO_4 measurements and because TSO_4 is a regional pollutant, cities were not divided into air pollution regions in analyses using this pollutant.

To ensure concurrency of outcome and air quality measurements, we distinguished between illnesses and symptoms during the previous year and those during the first 2 yr of life. Each health outcome was analyzed using air pollution measurements from the period corresponding to the health response. To assess the sensitivity of findings to the choice of air pollution measure, we also investigated the associations between lifetime mean air pollution concentration and illness and symptom responses of lifetime residents. For the analysis of pulmonary function values, both the mean concentrations during the previous year and, for lifetime residents, the mean lifetime concentration were considered.

Health Outcomes and Statistical Methods

Each child took home an explanatory letter, a permission request for a spirometric examination, and a questionnaire to be completed by a parent or guardian. Children were examined in school. They performed forced expiratory maneuvers on a water-filled recording spirometer (Warren E. Collins, Braintree, MA) while sitting with free mobility and without a noseclip. Additional details regarding the spirometric examination are provided elsewhere (13).

For this report, pulmonary function was measured by forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). The pulmonary function data were investigated by a 2-step multiple linear regression. First, the logarithm of each pulmonary function variable was regressed on sex and the logarithms of height, weight, and age as specified by a previously derived normative model (13), as well as maternal smoking status, 3 categories of parental education, and indicator variables for the 27 region-cohorts. The adjusted means of the pulmonary function variables were then computed for each region-cohort from the fitted model and analyzed in a second step described subsequently.

Six respiratory illness and symptom responses were evaluated. Five of these, bronchitis, persistent cough, persistent wheeze, respiratory illness, and the lower respiratory index, a composite variable defined as a positive response for either cough, bronchitis, or respiratory illness, were obtained at the second examination and referred to illnesses in the previous year. The sixth outcome was reported respiratory illness before 2 yr of age. The questionnaire-based definitions of these outcomes are given elsewhere (6).

The respiratory illness and symptom data were investigated by a 2-step logistic regression. At the first step, each regression model included the child's age and sex, parental edu-

cation, and maternal smoking level as reported at that examination. Previously reported analyses of these data had identified these variables, but not type of cooking stove, as associated with respiratory illness and symptom frequency (6). The regression coefficients obtained in this analysis were used to calculate the logit of respiratory illness or symptom frequency for each region-cohort, adjusted for age, sex, parental education, and maternal smoking. These adjusted logits were then analyzed in a second step described subsequently.

Preliminary analyses showed that variability among the region-cohort-specific mean pulmonary levels and adjusted logits was larger than would be expected given the between-individual variability of FVC, FEV_1, and respiratory symptoms. Thus, we fitted mixed linear models that included nested random effects for city, region, and year to the 27 group means. Likelihood ratio tests established, however, that the year and region variance components were not significantly greater than zero. That is, the overall variation of adjusted summary values between regions and years of study was consistent with sampling variability of pulmonary function measurements and respiratory illness responses. The variation in summary measures between cities, however, was larger than between-individual variation would predict. Thus, the children living within a given city gave consistent responses from year to year and from region to region, whereas differences between cities in mean health responses were larger than random fluctuation would predict. This phenomenon, sometimes called clustering or a design effect, is a common feature of survey data. To model this variability, all regression analyses reported here included a random effect for city, and standard errors of regression coefficients were adjusted accordingly. Although the regression coefficients can be interpreted in the usual way, the lack of independence among the observations required special estimation procedures. The 2-step method described in the *Appendix* avoided burdensome computing costs.

One possible source of city-to-city variability was the difference between cities in air quality. Despite the lack of evidence for excess variability within cities, we also investigated whether variability between examination years and between regions within the cities was associated with air pollutant concentrations. Specifically, in each analysis, we estimated both the association between mean health outcome and mean pollutant concentration for the 6 cities (the between-cities coefficient) and the association between year-to-year and region-to-region differences in health outcomes and air pollutant values within the 6 cities (the within-cities coefficient). Because only 2 cities, Steubenville and St. Louis, had substantial within-city variation in air pollutant concentrations, we replicated the within-city analyses for each of these cities separately. The high correlation between air pollutants made regression models with multiple pollutant variables uninformative, hence each pollutant was considered separately in a univariate analysis. Additional technical details regarding the stochastic models and estimation procedures are provided in the *Appendix*.

Results

Air Quality

During the first years of study, TSP and SO_2 concentrations declined substantially in St. Louis and Steubenville, the cities chosen because their historical air pollutant concentrations had exceeded annual and 24-h National Ambient Air Quality Standards (table 1). Relatively small changes in the concentrations of these pollutants were observed in the other 4 cities.

In St. Louis, Steubenville, and Kingston-Harriman, we defined 2 air pollution regions (table 1). In St. Louis, the regions were defined by proximity to a titanium pigment plant on the southern edge of the study area. In the area near the plant, Carondolet, SO_2 concentrations fluctuated with the level of production, which ceased completely in Jan-

TABLE 1

ANNUAL MEAN TSP, SO_2, AND TSO_4 CONCENTRATION FOR THE YEAR PRECEDING EACH EXAMINATION BY REGION AND YEAR OF STUDY

			Annual Mean		
City	Region	Year	TSP	SO_2	TSO_4
Portage, WI	Whole sample	76	48.4	11.0*	5.4†
		77	40.4	11.1*	5.4†
		78	32.0	11.4*	5.4†
		79	36.2	12.7*	5.4†
City mean			39.3	11.8	5.4
Topeka, KS	Whole sample	77	73.0	3.3	4.4
		78	59.5	2.9	4.5
		79	61.7	3.2	5.2
		80	57.9	4.2	7.5
City mean			63.0	3.4	5.4
Watertown, MA	Whole sample	74	41.9	16.2	9.3
		75	50.7	19.5	7.8‡
		76	42.6	13.9	8.7
		77	48.4	22.1	8.0
City mean			45.9	17.9	8.4
Kingston & Harriman, TN	Kingston	75	67.4	33.0*	10.5
		76	68.4	32.6*	8.5
		77	62.8	18.0*	9.3
		78	62.1	14.0*	9.8
	Harriman	75	56.5	29.6*	10.5
		76	57.6	40.6*	8.5
		77	62.6	17.1*	9.2
		78	56.3	12.5*	9.8
City mean			61.7	24.7	9.5
St. Louis, MO	Carondelet	75	129.3	89.6*	15.9
		76	125.7	184.0*	8.8
		77	103.9	88.2*	10.6
		78	104.8	31.9*	7.6
	Rest of sample	75	73.9	43.2	15.9
		76	69.6	31.7	8.8
		77	77.6	41.3	10.6
		78	69.9	36.4	7.6
City mean			94.3	68.3	10.7
Steubenville, OH	Valley	76	163.0	114.3	18.3
		77	150.3	77.9	18.4
		78	102.9	53.8	19.3
		79	116.9	75.1	19.3
	Ridge	76	99.9	NA	18.3
		77	105.6	64.7	18.4
		78	80.1	48.5	19.3
		79	94.1	50.2	19.3
City mean			114.1	60.6	18.8

Definition of abbreviations: TSP = total suspended particulates; TSO_4 = sulfate fraction of TSP.
* Continuous SO_2 monitors.
† TSO_4 estimated from period 1979 to 1980.
‡ One quarter of data estimated.

uary 1978 (14). Mean SO_2 concentrations subsequently dropped to values similar to those found elsewhere in the St. Louis metropolitan area. Differences between regions in TSP concentrations also declined during the period of health examinations but remained substantial in 1978. In Steubenville, the area designated as Valley is along the Ohio River and close to major pollution sources. The area labeled Ridge is about 100 m above the valley floor and more distant from these sources. Total suspended particle and SO_2 concentrations declined in the Valley between 1976 and 1979 as a result of control strategies and plant closings but were higher than concentrations along the Ridge during the entire period.

Kingston and Harriman, TN are approximately 8 km apart and are separated by a 100-m ridge. Air pollution concentrations were comparable in the 2 communities throughout the period of study. The 2 air pollution regions were determined by the geographic separation of the 2 communities rather than by an air pollution gradient.

The correlations between the means and ninetieth percentiles of the TSP and SO_2 distributions during the 1-yr periods preceding the 36 health examinations were 0.98 and 0.97, respectively. Thus, further analyses of pollutant concentrations during these 1-yr periods were based on the mean values. The correlation between mean TSP and mean TSO_4 concentrations for these periods was 0.70. The correlations of mean SO_2 concentrations with TSP and TSO_4 concentrations for the 35 examination periods that had SO_2 data were 0.81 and 0.54, respectively. When the second examination period in Carondolet was excluded, these correlations increased to 0.89 and 0.79, respectively. Thus, correlations between

TABLE 2

NUMBERS OF SUBJECTS AND REPORTED ILLNESS AND SYMPTOM RATES (PER 1,000) BY REGION AND YEAR OF STUDY*

City	Region	Year	Examination 1st	Examination 2nd	Illness Pre 2	Cough	Bronchitis	Chest Illness	LRI	Wheeze
Portage, WI	Whole Sample	76	701		242					
		77	656	629	207	65	57	99	157	85
		78	320	599	240	61	43	64	130	125
		79		251		92	45	87	174	116
Total			1,677	1,479		69	49	85	149	109
Topeka, KS	Whole sample	77	1,412		168					
		78	288	1,122	289	71	79	153	213	114
		79	207	177	281	68	64	137	209	103
		80		140		110	141	139	227	165
Total			1,894	1,439		74	83	150	213	117
Watertown, MA	Whole sample	74	613		—					
		75	384	525	160	48	48	165	212	57
		76	387	338	106	61	62	153	221	76
		77		304		49	52	101	147	96
Total			1,384	1,167		53	54	146	199	75
Kingston & Harriman, TN	Kingston	75	222		—					
		76	155	196	286	78	178	282	368	125
		77	201	120	146	100	132	267	369	113
		78		175		92	160	166	273	176
	Harriman	75	311		—					
		76	190	238	169	94	90	216	278	145
		77	177	158	167	130	143	226	372	105
		78		142		94	65	129	182	201
Total			1,256	1,029		99	133	219	309	148
St. Louis, MO	Carondelet	75	489		166					
		76	318	396	152	73	58	85	178	83
		77	94	211	95	123	85	95	217	111
		78		47		111	137	140	249	259
	Rest of sample	75	682		136					
		76	431	602	141	113	88	106	224	104
		77	103	335	167	99	79	100	213	110
		78		63		102	80	98	176	92
Total			2,117	1,654		102	80	99	209	106
Steubenville, OH	Valley	76	348		243					
		77	200	325	224	112	149	169	278	100
		78	233	174	148	140	115	176	325	144
		79		172		96	132	157	270	123
	Ridge	76	476		199					
		77	275	437	188	132	99	182	285	102
		78	246	243	137	165	140	207	325	167
		79		208		76	82	178	261	158
Total			1,778	1,559		125	121	179	290	128

Definition of abbreviations: LRI = lower respiratory illness.

* Rates are adjusted for sex, age, maternal smoking, and parental education.

TABLE 3

BETWEEN- AND WITHIN-CITY LOGISTIC REGRESSION COEFFICIENTS (× 1,000) FOR TSP, SO_2, AND TSO_4 CONCENTRATIONS (WITH STANDARD ERRORS) FOR RESPIRATORY ILLNESS AND SYMPTOM RATES*

	Between Cities			Within Cities		
	TSP	SO_2	TSO_4	TSP	SO_2	TSO_4
Cough	10.1 (1.8)†	9.1 (3.0)†	47 (16)†	−5.2 (2.7)	−3.0 (1.5)‡	85 (63)
Bronchitis	10.3 (4.6)‡	6.1 (5.1)	52 (26)‡	1.5 (2.6)	−2.3 (1.6)	52 (32)
Chest illness	3.9 (4.4)	−0.6 (4.3)	39 (23)	−1.8 (2.4)	−1.4 (1.4)	−86 (57)
Lower respiratory illness index	7.6 (3.5)‡	4.6 (3.6)	45 (19)‡	−2.1 (1.9)	−1.8 (1.1)	−3 (46)
Wheeze	2.8 (3.3)	1.1 (3.5)	13 (19)	−6.2 (2.6)†	−3.0 (1.4)‡	103 (57)

For definition of abbreviations, see table 1.
* All models include sex, age, maternal smoking, and parental education.
† $p < 0.01$.
‡ $p < 0.05$.

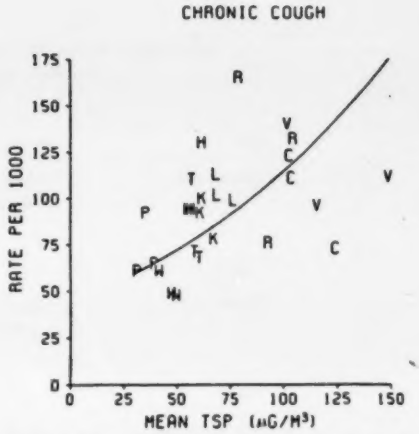

Fig. 1. Plot of adjusted frequency of cough for the 27 region-cohorts at the second examination against mean TSP concentration during the previous year, with between-cities regression equation. (P = Portage; T = Topeka; W = Watertown; C = Carondolet; L = Other St. Louis; R = Steubenville Ridge; V = Steubenville Valley; K = Kingston; H = Harriman).

the 3 measures of fossil fuel air pollution were uniformly high. In addition, mean TSP concentrations during the 1-yr periods were highly correlated with mean lifetime TSP concentrations and with TSP concentration during the first 2 yr of life.

Respiratory Illness and Symptom Rates

In total, 10,106 children between 6 and 9 yr of age were seen at the first examination. Of these, 8,380 children were seen approximately 1 yr later at the second examination. The sample at the second examination was limited to children 7 to 10 yr of age, resulting in the elimination from analysis of 44 children 6 yr old and 9 children 11 yr old and leaving 8,327 children available for analysis (table 2). Adjusted illness rates for the 6 illness and symptom outcomes were calculated for each of the 27 region-cohorts (table 2).

Regional and temporal variation of illness and symptom rates within the 6 cities was consistent with sampling variability. For the 5 outcomes recorded at the second examination, city-specific average illness and symptom rates were consistently largest in Kingston-Harriman and Steubenville (table 2). The between-cities regression coefficients for TSP, summarizing the association between mean TSP concentration in the previous year and adjusted illness and symptom rates across the 6 cities, were positive for all health outcomes (table 3). The odds ratios for illness rates associated with a 10 $\mu g/m^3$ difference in TSP concentration were: for cough, 1.11 ($p < 0.01$, see figure 1); for bronchitis, 1.11 ($p < 0.05$); for lower respiratory illness index, 1.08 ($p < 0.05$). (For a regression coefficient, b, given in tables 3 or 4, the relative odds associated with a 10-$\mu g/m^3$ difference in pollutant concentration is exp (10* b), which is approximately equal to 1 + 10b. The difference, 10 μ/gm^3, is arbitrary, but was chosen to be relevant to the range of differences in TSP concentrations found between pairs of cities.) Positive but nonsignificant associations were found for wheeze and chest illness. The same pattern of association was found in the regression analyses based on TSO_4 concentrations, except that regression coefficients were larger by a factor of 5 because of the differences in scale between TSP and TSO_4 concentrations. The analyses of SO_2 concentrations gave smaller regression coefficients, but the association remained significant for cough.

A different picture was provided by the within-city regression coefficients. Within-city variation in illness rates was negatively associated with TSP concentration for 4 of the 5 illness rates examined and was negatively associated with SO_2 concentration for all 5 health outcomes (table 3). The negative association achieved significance for wheeze and cough. Because the within-city regression coefficient was determined almost entirely by the data from St. Louis and Steubenville, we performed separate analyses for each of these cities (table 4). The regression coefficients were negative for 9 of the 10 analyses and comparable in magnitude to the within-city coefficients for all cities combined.

The within-city results for TSO_4 were more consistent with the between-city findings (table 3). Only 2 of the 5 within-city regression coefficients for TSO_4 were negative, and none of the regression coefficients was significantly different from zero. Because 2 regions in the same city were assigned the same TSO_4 values, this result indicates only an absence of temporal covariation of illness rates and TSO_4 concentrations in the 6 cities.

To examine the sensitivity of these results to the choice of air pollution metric, we restricted the sample to the subset of children who were lifetime residents of their city and used each child's mean lifetime TSP concentration. The between-city regression coefficients were consistently smaller in this analysis, reflecting the higher historical concentrations of TSP. The regression coefficient for cough was not significant in this analysis, otherwise the ratios of these

TABLE 4

CITY-SPECIFIC LOGISTIC REGRESSION COEFFICIENTS (× 1,000) FOR TSP, SO_2, AND TSO_4 CONCENTRATIONS (WITH STANDARD ERRORS) FOR RESPIRATORY ILLNESS AND SYMPTOM RATES*

	St. Louis			Steubenville		
	TSP	SO_2	TSO_4	TSP	SO_2	TSO_4
Cough	−6.1 (3.9)	−2.7 (1.5)	54 (98)	−4.1 (3.9)	−6.5 (7.7)	−50 (188)
Bronchitis	−6.3 (4.4)	−2.9 (1.7)	39 (108)	4.1 (3.7)	7.7 (7.8)	0 (189)
Chest illness	−3.5 (4.0)	−1.6 (1.5)	−39 (102)	−1.5 (3.3)	−3.2 (6.6)	−77 (162)
Lower respiratory illness index	−4.3 (3.0)	−1.9 (1.1)	19 (74)	−1.6 (2.8)	−3.5 (5.6)	1 (137)
Wheeze	−2.9 (3.7)	−2.4 (1.4)	−22 (96)	−7.7 (3.9)†	−17.7 (7.7)†	466 (188)†

For definition of abbreviations, see table 1.
* All models include sex, age, maternal smoking, and parental education.
† $p < 0.05$.

TABLE 5

GEOMETRIC MEAN FEV, AND FVC (L) VALUES FOR EACH REGION AND YEAR OF STUDY, ADJUSTED FOR SEX, AGE, HEIGHT, MATERNAL SMOKING, AND PARENTAL EDUCATION

			1st Examination		2nd Examination	
City	Region	Year	FEV,	FVC	FEV,	FVC
Portage, WI	Whole	76	1.409	1.607		
	Sample	77	1.459	1.662	1.618	1.858
		78	1.427	1.630	1.623	1.863
		79			1.581	1.818
Mean			1.432	1.633	1.607	1.846
Topeka, KS	Whole	77	1.381	1.559		
	sample	78	1.402	1.620	1.601	1.846
		79	1.417	1.634	1.577	1.810
		80			1.612	1.849
Mean			1.400	1.604	1.597	1.835
Watertown, MA	Whole	74	1.392	1.565		
	sample	75	1.405	1.578	1.563	1.758
		76	1.379	1.553	1.566	1.781
		77			1.553	1.773
Mean			1.392	1.565	1.561	1.771
Kingston &	Kingston	75	1.409	1.610		
Harriman, TN		76	1.411	1.604	1.603	1.822
		77	1.377	1.609	1.541	1.809
		78			1.559	1.792
	Harriman	75	1.368	1.585		
		76	1.404	1.624	1.580	1.821
		77	1.405	1.604	1.572	1.824
		78			1.558	1.806
Mean			1.396	1.606	1.569	1.812
St. Louis, MO	Carondelet	75	1.416	1.604		
		76	1.421	1.617	1.620	1.832
		77	1.418	1.638	1.583	1.831
		78			1.532	1.785
	Rest of	75	1.380	1.554		
	sample	76	1.421	1.615	1.591	1.808
		77	1.424	1.619	1.559	1.822
		78			1.587	.817
Mean			1.413	1.608	1.579	1.816
Steubenville, OH	Valley	76	1.423	1.598		
		77	1.408	1.602	1.587	1.819
		78	1.413	1.618	1.551	1.793
		79			1.593	1.818
	Ridge	76	1.418	1.594		
		77	1.427	1.610	1.582	1.807
		78	1.418	1.635	1.583	1.835
		79			1.595	1.843
Mean			1.418	1.610	1.582	1.819

coefficients to their standard errors changed very little. (Results not shown.) Four of the 5 within-cities coefficients were negative in this analysis and the coefficient for wheeze remained significant ($p < 0.05$). Thus, the results using lifetime mean TSP concentrations were similar to those using mean concentrations during the year preceding examination.

Only the Carondolet air pollution region provided information about substantial changes in SO_2 concentration not collinear with changes in TSP concentration. Annual mean SO_2 concentrations measured in Carondolet dropped from 184.0 $\mu g/m^3$ in 1976 to 88.2 $\mu g/m^3$ in 1977, whereas annual mean TSP concentrations changed only from 125.7 to 103.9 $\mu g/m^3$ (table 1). Illness rates, however, were consistently higher in 1977. For example, the adjusted frequency of reported cough was 73 per 1,000 in 1976 (95% CI, 50 to 104) and 123 in 1977 (95% CI, 83 to 177). Although these rates were not significantly different, the direction of these changes is not consistent with the hypothesis of a health benefit from these dramatic reductions in SO_2 concentration.

The reported history of childhood respiratory illness before 2 yr of age provided a respiratory health outcome potentially affected by exposures 4 to 9 yr before the health examination, when air pollution concentrations in the more polluted cities were much higher. For this outcome variable, the model that included the mean TSP concentration during the relevant 2-yr period for each lifetime resident gave estimated logistic regression coefficients of $-0.7 \pm 1.2 (\times 10^{-3})$ between cities and $8.7 \pm 3.9 (\times 10^{-3})$ ($p < 0.05$) within cities.

Pulmonary Function

Adjusted mean pulmonary function residuals varied substantially between cit-

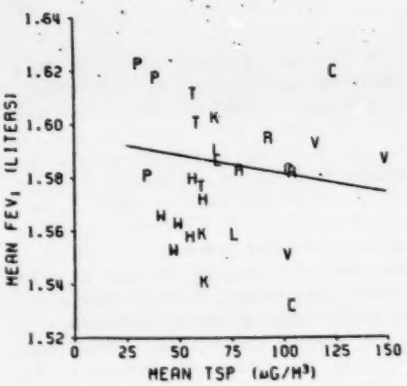

Fig. 2. Plot of adjusted mean percent of predicted FEV_1 at the first examination for the 27 region-cohorts against mean TSP concentration during the previous year, with between-cities regression equation. The slope is not significantly different from 0. See figure 1 for definition of abbreviations.

ies, but within-city variability was consistent with the between-individual variation of pulmonary function measurements (table 5 and figure 2). Neither the variation between cities nor the variation within cities was associated with TSP concentrations during the previous year (table 6). Between cities, for example, an increase of 10 $\mu g/m^3$ in TSP concentration was associated with an increase of $0.06 \pm 0.17\%$ in FEV_1 level at the first examination and a decrease of $0.09 \pm 0.17\%$ at the second examination. Even smaller coefficients were obtained for FVC level. The within-cities regression analysis gave a slightly larger positive association between TSP concentration and FEV_1, $0.08 \pm 0.08\%$ and $0.18 \pm 0.10\%$ per 10 $\mu g/m^3$ increase in TSP at the first and second examinations, respectively, but neither of these values achieved significance. The within-cities analysis gave consistently small coefficients for FVC. When this analysis was repeated for lifetime residents using lifetime TSP concentration, results were again uniformly negative. The regression analyses using TSO_4 and SO_2 concentrations also gave uniformly negative results.

Discussion

Among 10,106 white preadolescent children enrolled for 3 yr in a longitudinal study of air pollution and health, frequencies of cough, bronchitis, and lower respiratory illness during the 1-yr period prior to the second annual examination were significantly associated with TSP and TSO_4 concentrations during the same period. The estimated effects were substantial. For example, the estimated relative odds for cough in Steubenville and Portage, 2 cities with a difference in average annual mean TSP concentration prior to the second examination of 74.8 $\mu g/m^3$ (table 1), was 2.13, compared with an observed relative odds of 1.93 (table 2). Somewhat weaker associations were observed for SO_2 concentrations, but the differences in results for the 3 pollutants are almost entirely attributable to the relatively high SO_2 concentration for an examination period in Carondolet with relatively low illness and symptom rates. These associations persisted when the analysis was restricted to lifetime residents and air quality was expressed as the average over children in each region-cohort of the mean lifetime concentrations. These results suggest an increased risk of lower respiratory illness among children exposed to elevated concentrations of fossil fuel air pollutants.

Given the positive association between symptom prevalence and air pollution concentrations across cities, we would expect to find a positive association within the cities with substantial year-to-year and regional variation in air pollution concentrations. Negative associations were found, however, between year-to-year and region-to-region variation in illness rates and air pollutant concentrations within the 6 cities. When the analysis was repeated with lifetime mean concentration of TSP for each lifetime resident, the within-city results were essentially unchanged. Thus, even though the within-cities regression coefficients were not, in most cases, significantly different from the between-city coefficients, the within-city results did not provide additional evidence in support of an air pollution effect.

The between-city results may represent differences in the samples between cities that are unrelated to air pollution exposure. For example, the cities visited in the spring tended to have both higher illness and symptom rates and higher air pollutant values, hence the positive associations may be attributable in part to better recall of illnesses in the previous winter when questionnaires were administered at the end of the winter season (spring surveys) compared with those administered in the fall. We have revised our questionnaire administration schedule to investigate this possibility. Other potential confounders include differences in interpretation of the questionnaire by the respondent and persistent differences in illness or reporting rates associated with ethnic or cultural factors.

No between-city association was found between reported respiratory illness before the age of 2 and TSP values corresponding to the period during which the illness would have occurred. Although this outcome may be more substantially affected by imperfect recall or mobility than by responses pertaining to recent experience, the concentrations corresponding to the early years of these children's lives were in many areas far greater than recent concentrations.

Pulmonary function also varied substantially among cohorts, but this variation was not associated with TSP, SO_2, or TSO_4 concentrations.

Because National Ambient Air Quality Standards for TSP and SO_2 concentrations have been in place for many years and because the air pollution data base relevant to the early examinations in this study consists almost entirely of TSP, TSO_4, and SO_2 measurements, the results presented here represent an important part of the available evidence regarding the health effects of fossil fuel air pollutants. The established relationship between fine particle sulfur mass and fine particle mass as measured by dichotomous samplers and X-ray fluorescence (15) implies that similar associations would have been obtained had fine particulate measurements been available for this period. Spatial averaging of pollutant concentrations across the defined regions is justified because the precise location of a child within the region is not known, and because the ambient concentrations reported from our network of indoor/outdoor stations were similar within these regions (11, 12).

Estimates of air pollution exposure based on TSP, TSO_4, and SO_2 concentrations recorded at outdoor stations have important limitations that are by now widely recognized. Nevertheless, all of these measures are considered reasonable surrogates for the ambient air pollutant

TABLE 6

BETWEEN- AND WITHIN-CITY REGRESSION COEFFICIENTS ($\times 10^4$) FOR TSP CONCENTRATION (WITH STANDARD ERRORS) IN MODELS FOR PULMONARY FUNCTION MEASUREMENTS AT THE FIRST AND SECOND EXAMINATIONS*

	Between-Cities	Within-Cities
First Examination		
log FEV_1	6.1 (16.9)	8.1 (8.1)
log FVC	2.0 (20.7)	0.0 (7.7)
Second Examination		
log FEV_1	−9.1 (17.1)	18.4 (10.4)
log FVC	−3.2 (24.0)	3.2 (10.1)

* All models include sex, age, height, maternal smoking, and parental education.

concentrations resulting from the emissions associated with fossil fuel combustion. Measures of inhalable particles and their chemical constituents are regarded as more relevant than are TSP to respiratory health effects. Exposure estimates may be further improved by the collection of indoor measurements. We have previously reported on the health effects of indoor exposures (6) and on the measurement of inhalable particles and their constituents (15).

The results of this analysis, therefore, leave substantial uncertainty regarding the health significance of the TSP and SO_2 exposures seen in the contemporary United States. Our results suggest that exposure to elevated concentrations of fossil fuel air pollution could be associated with substantially increased risk of bronchitis and other lower respiratory disorders in preadolescent children.

The lack of association between pollutant levels and pulmonary function may be explained by the fact that the measures used, FEV_1 and FVC, lack sufficient specificity to identify early changes in airways that might be associated with the lower respiratory symptoms reported. Efforts to identify early or acute effects of air pollutants have been, for the most part, directed toward effects on airways. Direct measures of airway resistance have been used in controlled clinical exposure to detect changes associated with SO_2 exposure in asthmatic subjects (16). Alternatively, responsiveness to bronchoconstrictive agents as measured by changes in FEV_1 before and after exposure to SO_2 has been required to demonstrate effects in normal subjects, and generally these studies have been conducted with concentrations of SO_2 considerably higher than those seen in the general environmental setting.

Early changes from both active (17) and passive (18, 19) cigarette smoking in children may affect FEV_1. These changes, however, are easier to demonstrate using measures that may more directly reflect changes in small airways (e.g., flow at middle to low lung volumes). Similarly, acute changes from exposure to summertime episodes of haze (O_3 and SO_4) have been demonstrated with various measures of flow such as peak expiratory flow (20) and MMEF/VC (21) rather than with FEV_1 and FVC. Thus, the absence of an association between pollutant levels and FEV_1 and FVC measurements in our cohort does not rule out the possibility that airways may be affected in these children. It does suggest, however, that in terms of accumulated growth of both lungs and airways, ambient exposures in children younger than 10 yr of age have not produced significant impairment in the children under study. Alternatively, despite an effect on symptoms, there may be no effect on pulmonary function. In the study of Vedal and coworkers (22) in 4,000 children from western Pennsylvania, no effect of SO_2 concentration was found on FVC, FEV_{75}, FEF_{25-75}, V_{max75}, and V_{max50}.

Analysis of later examinations will focus on the extent to which variation in illness rates can be reduced by inclusion of other pollutant variables as explanatory measures. In addition, future analyses will focus on longitudinal measures of respiratory health derived from repeated examinations of the participating children and measures of pulmonary function that are more sensitive to changes in airways. The most important requirement for strengthening the evidence regarding the health effects of air pollutants, however, is further disaggregation of the exposure groups. This objective is being addressed through increased emphasis on monitoring of homes and schools to provide data for individualized estimation of exposure to monitored pollutants, including fine particles and NO_2. With this further disaggregation of exposure and continued evaluation of these children as they move through adolescence, we should be in a position to assess the magnitude of pollutant effects that can be anticipated in the 1980's.

Appendix

The pulmonary function measurements were analyzed using mixed linear models of the form

$$\ln(PF_{ijk}) = \alpha + \beta_1 AP_{i..} + \beta_2(AP_{ijk} - AP_{i..}) + \gamma_i + \varepsilon_{ijk}$$

where $\ln(PF_{ijk})$ is the adjusted mean log pulmonary function value for children seen in year k in region j of city i, AP_{ijk} is the air pollution concentration applicable to that region-cohort, and $AP_{i..}$ is the average of the pollutant concentrations for city i over regions and cohorts. The random effects in this model are γ_i, the city effect, and ε_{ijk}, which represents the measurement error or between-individual variability. The fixed regression coefficients are β_1, the between-cities regression of pulmonary function level on air pollutant concentration, and β_2, the within-cities coefficient. The adjusted means were obtained from a first-stage linear regression analysis, which also produced estimates of $var(\varepsilon_{ijk})$. This model was fitted by the method of maximal likelihood, with the error variances treated as known and set to the estimates obtained in the first-stage regression. The likelihood was maximized by a Gauss-Newton procedure. Variances of estimated regression coefficients were obtained from the inverse of the estimated information matrix. To test for heterogeneity of the within-city regression coefficients, a second set of models was fitted in which β_2 was treated as a random effect with unknown mean and variance; however, the estimate of this variance component was zero or quite small in every instance. Thus, we report a single within-cities regression coefficient.

The analyses of respiratory illness and symptom rates were similar to those of the pulmonary function measurements, except that the dependent variable was the adjusted logit from the initial logistic regression. As with the linear model, the error variance was estimated as the variance of the corresponding linear combination of regression coefficients.

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